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Mucositis after Reduced Intensity Conditioning and Allogeneic Stem Cell Transplantation

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Keywords

Allogeneic stem cell transplantation · Conditioning therapy · Mucositis · Transplant-related morbidity · Toxicity

Summary

Background: Therapy-related mucositis is associated with considerable morbidity. This complication following allogeneic stem cell therapy (allo-SCT) is less severe after reduced intense conditioning (RIC); however, even here it may be serious. **Methods:** 52 patients (male: n = 35 (67%), female: n = 17 (33%)) at a median age of 62 years (35–73 years) underwent allo-SCT after RIC. Conditioning was either total body irradiation $(TBI)_{2Gy}$/±fludarabine (n = 33, 63.5%) or chemotherapy based. Graft-versus-host disease (GvHD) prophylaxis was carried out with cyclosporine A ± mycophenolate mofetil (MMF). 45 patients (87%) received short-course methotrexate (MTX). Mucositis was graded according to the Bearman and the World Health Organisation (WHO) scale. A variety of parameters were correlated with mucositis. **Results:** The Bearman and WHO scales showed excellent correlation. Mucositis was significantly more severe after chemotherapy-based conditioning compared to conditioning with TBI_{2Gy}/±fludarabine ($p < 0.002$) as well as in cases with an increase in creatinine levels above the upper normal value (UNV) on day +1 after SCT ($p < 0.05$). Furthermore, the severity correlated with time to engraftment of leucocytes (correlation coefficient (cc) = 0.26, $p < 0.02$) and thrombocytes (cc = 0.38, $p < 0.001$). **Conclusions:** The conditioning regimen and increased creatinine levels at day +1 were identified as factors predicting the severity of mucositis after RIC-SCT. Creatinine levels on day +1 after SCT may help identify patients at risk for severe mucositis in the further course of transplantation.

Schlüsselwörter

Allogene Stammzelltransplantation · Konditionierung · Mukositis · Transplantationsassoziierte Morbidität · Toxizität

Zusammenfassung

Hintergrund: Die therapieassoziierte Mucositis nach allogener Stammzelltransplantation (allo-SCT) verläuft nach dosisreduzierter Konditionierung (RIC) im Allgemeinen milder als nach myeloablativer Konditionierung, aber auch hier sind sehr schwere Verläufe möglich. **Methoden:** 52 Patienten (männlich: n = 35 (67%), weiblich: n = 17 (33%)) mit einem medianen Alter von 62 Jahren (35–73 Jahre) wurden nach RIC einer allo-SCT unterzogen. Zur Konditionierung wurden entweder Ganzkörperbestrahlung $(TBI)_{2Gy}$/±Fludarabin (n = 33, 63,5%) oder rein Chemotherapie-basierte Protokolle eingesetzt. Die Graft-versus-Host Disease (GvHD)-Prophylaxe erfolgte mit Cyclosporin-A ± Mycophenolat-Mofetil (MMF). 45 Patienten (87%) erhielten zusätzlich «short-course» Methotrexat (MTX). Die Graduierung der Mucositis erfolgte gemäß der Bearman-Skala und dem Schema der Weltgesundheitsorganisation (WHO). Eine Reihe klinischer und paraklinischer Parameter wurde auf eine Korrelation mit dem Schweregrad der Mucositis untersucht. **Ergebnisse:** Die Bearman- und WHO-Skalen zeigten eine exzellente Korrelation. Der Grad der Mukositis war nach rein Chemotherapie-basierter Konditionierung signifikant höher als bei Einsatz von TBI_{2Gy}/±Fludarabin ($p < 0,002$), wie auch bei Patienten mit einem Anstieg des Kreatinin-Levels über den oberen Normwert am Tag +1 nach SCT ($p < 0,05$). Darüber hinaus korrelierte die Schwere der Mucositis mit der Zeitdauer bis zum Engraftment der Leukozyten (Korrelationskoeffizient (cc) = 0,26, $p < 0,02$) und der Thrombozyten (cc = 0,38, $p < 0,001$). **Schlussfolgerungen:** Die Art der Konditionierung und ein erhöhter Serumkreatinin-Level am Tag +1 nach der Transplantation wurden als die Parameter identifiziert, die mit einem schwereren Verlauf der Mucositis korrelieren.

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Introduction

Oral mucositis contributes significantly to the morbidity of patients undergoing allogeneic stem cell transplantation (SCT) [1]. The degree of mucositis may vary from mild enanthema to ulcerative disease requiring continuous infusion of narcotics and total parenteral nutrition. In patients undergoing SCT after myeloablative conditioning therapy, cases requiring intubation due to swollen mucosa or even lethal courses have been described [2]. In addition to an inferior clinical course of patients with severe mucositis, the consumption of resources and the increased amount of hospital charges correlate with the degree of mucositis [1].

Approaches to reduce the intensity of mucositis include measures such as a stringent mouth care and oral hygiene. The prophylactic administration of human recombinant keratinocyte growth factor (palifermin) can be considered in cases of myeloablative total body irradiation (TBI)-based conditioning [3]. Other investigators have described positive effects of crushed ice in the mouth for approximately 6 h under high-dose therapy compared to conventional mouth rinses with salinic solution [4].

The introduction of so-called reduced intensity conditioning (RIC) protocols in the preparation for allogeneic SCT is an approach to reduce the toxicity of the conditioning therapy and to make allogeneic SCT also available for heavily pretreated or elderly patients [5]. SCT after RIC is more successful for the treatment of less aggressive disease such as myelodysplastic syndromes, indolent lymphomas or multiple myeloma than for aggressive entities like acute leukaemias since the graft-versus-leukaemia effect requires several weeks before becoming active [5, 6]. However, RIC includes a variety of protocols consisting of either chemotherapy alone or in combination with a low-dosed TBI of 2 Gy. Furthermore, the intensity of these protocols varies broadly. More intense protocols include melphalan, busulphan or treosulfan in conjunction with fludarabine, and the mildest variant consists of TBI_{2Gy}/±fludarabin [7, 8]. Regimen-related mucositis after RIC has been described to be less intensive than after myeloablative conditioning; however, in some cases, even after RIC a severe mucositis may occur for unknown reasons.

Short-course methotrexate (MTX) consisting of application on days +1, +3 and +6 is the gold standard in graft-versus-host disease (GvHD) prophylaxis after myeloablative conditioning therapy [9]. The use of MTX for GvHD prophylaxis after dose-reduced conditioning varies between different protocols [10]. A significant contribution of MTX used for GvHD prophylaxis to the intensity of mucositis during pancytopenia has been shown [11]. MTX is metabolised in the liver, and the drug and its derivates are excreted by the kidneys. Hepatotoxicity varying from mild elevation of the laboratory parameters to fibrosis is a known side effect of MTX therapy. Fibrosis has even been described after long-term administration of MTX in low doses [12]. As a consequence, a dose reduction of MTX given for GvHD prophylaxis depending on an elevation of the unconjugated bilirubin at day +1 has become common practice in allogeneic SCT. However, this approach has so far not been validated in clinical trials. Another way to reduce the toxicity of MTX is the concomitant administration of folic acid, especially in high-dose protocols [13]. Robien et al. [14] have shown recently that this approach has no positive or negative effects on the clinical course after allogeneic SCT and on GvHD prophylaxis with MTX. An impairment of kidney function is a common indication to reduce or discontinue calcineurin inhibitors; however, it has so far no influence on the MTX dose.

The identification of factors correlating with the severity of therapy-related mucositis after RIC and allogeneic SCT was the intention of the present investigation. Most factors investigated were selected on the basis of their presence not later than day +1 after transplantation. The reason for this policy was the aim to identify possible factors predicting a more severe mucositis during the later course of transplantation. Data from 52 consecutive patients were available for this analysis.

Patients and Methods

Patients, Diagnoses and Transplantations

Between December 2005 and October 2008 52 patients underwent allogeneic SCT after RIC at our institution. 35 patients (67.3%) were male and 17 patients (36.7%) were female. The median patient age was 61.6 years, ranging from 34.9 to 72.6 years. The underlying diagnoses are shown in table 1. Most patients were intensively pre-treated with 5.5 (median, range 0–27) cycles of chemotherapy. Only 1 patient was chemotherapy naive. 12 patients (23.1%) had a history of preceding high-dose therapy followed by autologous stem cell re-infusion.

In 4 cases (7.7%) a human leucocyte antigen (HLA)-identical sibling was available for stem cell donation. The vast majority of patients (92.3%) was transplanted from an unrelated donor. At most 1 full mismatch was present in 9 cases (17.3%). 71.2% (n = 37) of the recipients and 59.6% (n = 31) of the donors had serologically documented preceding

Table 1. Diagnoses

Diagnosis	n	%
Acute myeloid leukaemia	19	36.5
Non-Hodgkin's lymphoma (indolent)	8	15.4
Multiple myeloma	7	13.5
Chronic lymphatic leukaemia	6	11.5
Non-Hodgkin's lymphoma (aggressive)	6	11.5
Myelodysplastic syndrome	3	5.8
Acute lymphatic leukaemia	1	1.9
Hodgkin's lymphoma	1	1.9
Myeloproliferative syndrome	1	1.9

Table 2. Conditioning regimen

Regimen	n	%
TBI-fludarabine	33	63.5
Treosulfan-fludarabine	12	23.1
Melphalan-fludarabine	5	9.6
Busulphan-fludarabine	1	1.9
Cyclophosphamide-fludarabine	1	1.9

Table 3. Factors with a probable or possible correlation with mucositis

Factor	Direct parameters	Surrogate parameters
Cumulative toxicity/regenerative capacity	preceding cycles of chemotherapy (n); preceding high-dose therapy + autologous SCT	age at transplantation
Intensity of conditioning therapy	minimal conditioning (2 Gy/flu) vs. other RIC regimens; use of ATG	
Type of SCT	related donor vs. unrelated donor; fully matched (6/6) vs. HLA mismatch	
Impaired renal excretion	creatinine level; creatinine increase; creatinine clearance (each after conditioning)	weight gain under conditioning; use of diuretics at day +1
Impaired hepatic function	increase of bilirubin; increase of transaminases; decrease of albumin	weight gain under conditioning; use of diuretics at day +1
Interaction with drugs	use of voriconazole for anti-mycotic prophylaxis	
Time to engraftment	leucocyte engraftment; thrombocyte engraftment	

SCT = Stem cell transplantation, flu = fludarabine, ATG = anti-thymocyte globulin, HLA = human leucocyte antigen, RIC = reduced intensity conditioning.

exposition to human cytomegalovirus. Only 1 (1.9%) patient was negative for herpes simplex virus (HSV).

The reasons for choosing an RIC protocol were at least one from the following list: patient's age, underlying diagnosis, history of pre-treatment and patient's clinical constitution or medical history. Table 2 shows the conditioning regimens. Nearly 2/3 of the patients (n = 33, 63.5%) were conditioned with TBI (2 Gy) and fludarabine (30–150 mg/m^2) [15]. 12 patients received treosulfan (36 g/m^2) and fludarabine (150 mg/m^2). 5 patients suffering from multiple myeloma were conditioned with melphalan (100–140 mg/m^2) and fludarabine (150 mg/m^2) [7, 16]. Busulphan (8 mg/kg) or cyclophosphamide (120 mg/kg) in conjunction with fludarabine (150 mg/m^2) were each given for preparation in 1 case (1.9%) [17]. In addition, 44 patients (84.6%) received anti-thymocyte globulin for prophylaxis of GvHD.

All patients received cyclosporine A intravenously; short-course MTX (15 mg/m^2 on day +1, 10 mg/m^2 on days +3 and +6) was given in 45 cases (86.5%). Cyclosporine A in conjunction with mycophenolate mofetil (MMF) was given after conditioning with TBI_{2Gy}/fludarabine [8]. In general, it was scheduled to discontinue GvHD prophylaxis between days +100 and +120.

Supportive Therapy

Five (9.6%) patients received palifermin for the prevention of severe mucositis after a history of high-dose therapy and autologous SCT. Antimicrobial prophylaxis followed common standards [18]. Parenteral nutrition was performed from the beginning of neutropenia until engraftment, and mouth care was carried out as described previously [19]. Morphine was given as continuous infusion when necessary.

Grading of Mucositis and Correlation to Clinical and Laboratory Parameters

Mucositis was graded daily according to both the Bearman and the World Health Organisation (WHO) scales, and the maximum value was used for further analyses. It has been known that the toxicity of anti-neoplastic therapy influences the degree of mucositis and that different regimens have different tropism of toxicity.

The hypothesis of the current investigation was that the severity of mucositis can be influenced by the following factors and that there are candidate factors that can predict a more intense manifestation of mucositis.

Direct and indirect parameters were chosen from the following categories:

- intensity of conditioning therapy,
- history of preceding therapy as a parameter for cumulative toxicity,
- factors indicating an increased overall toxicity or an impaired excretion capacity for drugs and their metabolites (e.g. bilirubin, transaminases, renal function),
- drugs that could interact with the MTX metabolism (e.g. use of voriconazole),
- additional preconditions with a possible association with the severity of mucositis (e.g. seropositivity for HSV).

The direct and indirect parameters are shown in table 3.

Data Collection and Analysis

Data were collected with the database software Access (Microsoft, Munich, Germany) and analysed using the computer software Excel (Microsoft) and GraphPad Prism for Windows (GraphPad Software, San Diego, CA, USA). The independent t-test or the Mann-Whitney U-test was used for the comparison of 2 groups, and datasets with more than 2 subgroups were compared by variate analysis. Correlations were identified by Spearman's rank correlation (SRC) test. Other tests are listed where appropriate.

Results

All patients showed engraftment with 1.0 leucocytes/nl at 16 days (median, range 0–31 days) after allogeneic SCT. The median time to 20 thrombocytes/nl independently from transfusions was 18.5 days (range 0–138 days). In 5 cases without recovery of thrombocytes, the data were censored for statistical reasons at the date of last follow-up.

Overall Grade of Mucositis

The overall incidence of oral mucositis was 44.2% (23/52). In patients with mucositis, it could be graded to 2 (median, range 1–3) according to the Bearman scale and to 3 (median, range 1–4) according to the WHO scale. Both scales for the grading of mucositis showed an excellent correlation (correlation coefficient (cc): 0.95, $p < 10^{-20}$, SRC); details are shown in table 4.

Cumulative Toxicity, Age and Severity of Mucositis

The influence of the intensity of prior anti-neoplastic therapy in relation to the severity of the mucositis after SCT was

investigated. 12 (23.1%) patients had a history of preceding high-dose therapy followed by SCT. The median intensity of mucositis according to the WHO scale was identical to 0 (range 0–4) in patients with and without prior high-dose therapy + SCT.

The majority of patients were heavily pre-treated with a median of 5.5 cycles (range 0–27) of conventional anti-neoplastic chemotherapy. The severity of mucositis did neither correlate with the number of preceding chemotherapy cycles nor with the interval from the last therapy cycle to transplantation. Even the patient's age at the time of transplantation had no influence (SRC).

Conditioning Therapy

Thirty-three patients (63.5%) were conditioned with a minimal-intensity regimen consisting of TBI_{2Gy} and fludarabine, and 19 patients received a chemotherapy-based RIC (36.5%). The incidence of mucositis was 27.3% (9/33) in the minimal conditioning group and 73.7% (14/19) in the chemotherapy-based conditioning group ($p < 10^{-8}$, Chi-square test). Also the degree of mucositis was significantly higher after chemotherapy-based conditioning. The degree was 0 (median, range 0–3) vs. 2 (median, range 0–3) according to the Bearman scale and 0 (median, range 0–4) vs. 3 (median, range 0–4) according to the WHO scheme. The difference was highly significant for both scales ($p < 10^{-3}$, Mann-Whitney U-test) (table 5, fig. 1).

After treosulfan-based conditioning, compared to non-treosulfan-based chemoconditioning, the degree of mucositis was 1.5 (median, range 0–3) vs. 2 (median, range 0–2) according to the Bearman scale and 3 (median, range 0–4) vs. 3 (median, range 0–4) according to the WHO scheme (p = 0.93, Mann-Whitney U-test).

GvHD Prophylaxis with MTX

Short-course MTX was part of the GvHD prophylaxis in 45 patients (86.5%). At 0 (range 0–4, WHO-scale), the median severity of mucositis was identical in patients with and without short-course MTX. However, there was a trend to a

Table 4. Grading of mucositis according to the Bearman scale (vertical) and to the WHO scale (horizontal). Each field contains the number of patients

WHO ➡	0°	I°	II°	III°	IV°
Bearman ⬇					
0°	29	1	1	–	–
I°	–	4	3	–	–
II°	–	–	1	3	7
III°	–	–	–	–	3
IV°	–	–	–	–	–

Table 5. Factors investigated for correlation with the severity of mucositis

Parameter	Analysis	p
Factors *without* correlation		
Preceding cycles of chemotherapy	Q	n.s.
Preceding high-dose therapy + autologous SCT	Y/N	n.s.
Numerical age at day of transplantation (years)	Q	n.s.
Matched-related donor SCT vs. unrelated donor SCT	Y/N	n.s.
Use of ATG within conditioning	Y/N	n.s.
Cytomegalovirus seropositivity of patient	Y/N	n.s.
Cytomegalovirus seropositivity of donor	Y/N	n.s.
Body weight prior to conditioning[a)]	Q	n.s.
Body weight at day +1[b)]	Q	n.s.
Weight gain from [a)] to [b)]	Q, Y/N	n.s.
Creatinine clearance prior to conditioning	Q	n.s.
Creatinine clearance at day +1 (valid for WHO grading only)	Q	n.s.
Serum creatinine level at day +1	Q	n.s.
Administration of diuretics at day +1	Y/N	n.s.
Serum albumin level at day +1	Q	n.s.
Serum level of bilirubin, GPT or GOT at day +1	Q	n.s.
Bilirubin, GPT or GOT > UNV at day +1	Y/N	n.s.
Voriconazole vs. fluconazole or itraconazole for anti-mycotic prophylaxis	Y/N	n.s.
Factors *correlating* with severity of mucositis		
2 Gy/flu-based minimal conditioning vs. other	Y/N	$p < 10^{-3}$, Mann-Whitney U-test
Creatinine > UNV at day +1	Y/N	p < 0.04, Mann-Whitney U-test
Creatinine clearance at day +1 (valid for Bearman grading only)	Q	cc: –0.27, p < 0.03, SRC
Days from SCT to leucocyte engraftment (L > 1.0/nl)	Q	cc: 0.26, p < 0.04, SRC
Days from SCT to thrombocyte engraftment (TC > 20/nl)	Q	cc: 0.38, p < 0.003, SRC

Y/N: Parameters were compared on a quantitative (yes/no, pathological/normal, positive/negative) basis.

Q: Parameters were compared on a qualitative (degree [%] of elevation, interval-scaled parameters) basis.

SCT = Stem cell transplantation, ATG = anti-thymocyte globulin, GOT = glutamate-oxalacetate transaminase, GPT = glutamate-pyruvate transaminase, UNV = upper normal level, n.s. = not significant, cc = correlation coefficient, SRC = Spearman's rank correlation, L = leucocytes, TC = thrombocytes.

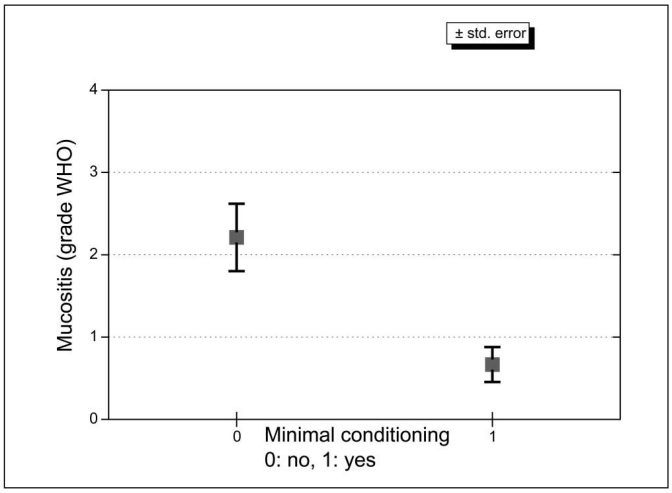

Fig. 1. WHO grade of mucositis in patients after minimal intense conditioning (0, left) and other RIC (1, right) prior to allogeneic SCT.

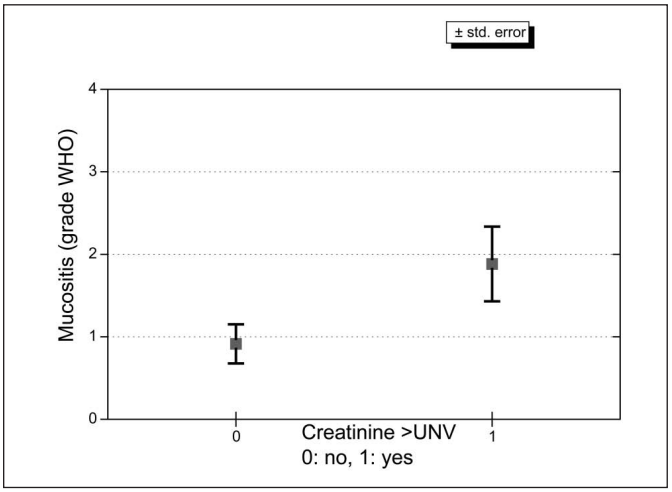

Fig. 2. WHO grade of mucositis in patients with normal (0, left) and elevated (1, right) serum creatinine levels at day +1.

higher degree of mucositis after MTX administration compared to patients who received no MTX (p = 0.16, Mann-Whitney U-test).

Parameters of Renal Function

At day +1 17 of 52 patients (32.7%) had a creatinine level above the upper normal value (UNV). These patients experienced a significantly higher degree of mucositis compared to patients with normal creatinine level: 0 (median, range $0–3_{[Bearman]}/4_{[WHO]}$) vs. 1 (median, range $0–3_{[Bearman]}/4_{[WHO]}$) (table 5, fig. 2). A significant correlation was found between a decreased creatinine clearance at day +1 and the maximal degree of mucositis graded according to the Bearman scale (cc: –0.27, $p < 0.03$, SRC). The degree of mucositis did not correlate with weight gain or an increase in creatinine from the day prior to conditioning until day +1, or with application of diuretics at day +1.

Parameters of Liver Function

Bilirubin, transaminase and albumin levels on day +1 were chosen as parameters of the liver function and liver toxicity due to conditioning therapy. Bilirubin was elevated in 27 cases (51.9%), glutamate-pyruvate transaminase (GPT) in 24 cases (46.2%) and glutamate-oxalacetate transaminase (GOT) in 14 cases (26.9%). Serum albumin levels were decreased in 44 cases (84.6%). For none of these parameters, a correlation between pathological values and the maximal degree of mucositis, neither by qualitative (normal vs. pathological) nor by quantitative analysis, was found (table 5).

Other Parameters

Voriconazole interacts with the metabolism of a variety of other drugs, e.g. cyclosporine A. 36 patients (69.2%) received voriconazole for anti-mycotic prophylaxis or therapy after transplantation, and 16 patients (30.8%) did not. There was no correlation between the administration of voriconazole and the maximal degree of mucositis.

Significant correlations were found for the time to engraftment of leucocytes (> 1.0 leucocytes/nl) (cc: 0.26, $p < 0.04$, SRC) and thrombocytes (> 20/nl, independently of transfusion) (cc: 0.38, $p < 0.003$, SRC). This statement is true for both gradings of mucositis, Bearman and WHO.

Discussion

RIC makes allogeneic SCT available for patients who are ineligible for myeloablative therapy [20, 21]. One important issue is the reduction of the cumulative toxicity in heavily pretreated patients. However, therapy-related mucositis occurs at a variable degree, even after reduced or minimal conditioning. The application of palifermin may be able to reduce the severity of mucositis after classical TBI-based conditioning; however, it must be initiated prior to conditioning, it is a very cost-intensive measure and its benefit has been discussed controversially [3]. Another option is a dose reduction or avoidance of MTX in GvHD prophylaxis. This investigation was performed to identify patients at higher risk for toxic mucositis not later than day +1 after allogeneic SCT.

Mucositis Bearman II° is common after myeloablative conditioning, and higher degrees may occur [22]. In contrast, only 14/52 (27%) of the patients presented here experienced a ≥ II° mucositis. However, our investigation clearly shows that mucositis is a relevant problem after RIC, since nearly 20% of patients exhibited a mucositis of WHO grade IV (table 4). The wide range between the absence and the different degrees of mucositis can only in part be explained by the choice of conditioning therapy: The median degree of mucositis was significantly higher after chemotherapy-based conditioning compared to minimal conditioning; however, even

after TBI_{2Gy}-based conditioning therapy, severe courses of mucositis were observed (table 5, fig. 1).

Cumulative toxicity and patient's age are common reasons for choosing an RIC protocol for conditioning, since increased organ toxicity of anti-neoplastic therapy has been described for elderly patients and for patients after intensive pre-treatment [20, 21]. In addition, cumulative toxicity after multiple cycles of conventional chemotherapy can lead to an impairment of cardiac function or to insufficiency of haemopoiesis [23]. Surprisingly, this experience cannot be easily transferred to the manifestation of mucositis after RIC. Neither the number of preceding chemotherapy cycles, a history of high-dose therapy nor the patient's age correlated with the intensity of mucositis.

Increased laboratory parameters of liver and kidney function prior to conditioning therapy did not predict a more severe course of mucositis. The only parameter with influence on the course of mucositis available prior to transplantation is the intensity of conditioning therapy.

Short-course MTX for GvHD prophylaxis worsens the mucositis after allogeneic transplantation [11]. However, after RIC transplantation, MTX is variably used in different protocols and a replacement by MMF is either an alternative or fixed in some protocols. To investigate the possibility to influence the severity of mucositis by adjustment of the dose or omitting MTX, a variety of parameters present at day +1 prior to the first MTX dose were investigated: Only a serum creatinine level above the UNV was a predictor of a more severe course of mucositis. No correlation was found between other parameters of kidney or liver function and the degree of mucositis.

The use of voriconazole for anti-fungal prophylaxis has become common practice in allogeneic SCT [24]. Intensive interactions with the metabolism of cyclosporine A have been described; data for other drugs are rare. A correlation between the use of voriconazole and mucositis was not found. The observation that a prolonged engraftment correlates with a worse course of mucositis may be in part explained by the fact that intact granulocytes are mandatory for inhibition and eradication of microbial invasion of the damaged mucosal areas.

In conclusion, in this study, 2 parameters correlated with the severity of mucositis after allogeneic SCT using RIC: the choice of the conditioning therapy and an elevated serum creatinine level at day +1.

After minimal conditioning with TBI_{2Gy}/fludarabin, a severe course of mucositis is rare. Based on the elevation of creatinine at day +1, a reduction or a replacement of MTX for GvHD prophylaxis could be an option to reduce the expected severity of mucositis. However, since MTX is a standard compound of GvHD prophylaxis, a dose reduction could lead to a higher incidence or severity of acute GvHD with enhanced morbidity and mortality.

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Disclosure Statement

The authors declare that they do not have to disclose any conflict of interest.

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